Spivack 10/532,114 31/08/2006

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L19 ANSWER 1 OF 7 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2006:522777 HCAPLUS
TITLE: Comparison of the effects of fasting morning, fasting evening and fed bedtime administration of **tenatoprazole** on intragastric pH in healthy volunteers: a randomized three-way crossover study
AUTHOR(S): Thomson, A. B. R.; Cohen, P.; **Ficheux, H.**; Fiorentini, P.; Domagala, F.; **Homerin, M.**; **Taccoen, A.**
CORPORATE SOURCE: Department of Medicine, Division of Gastroenterology, University of Alberta, Edmonton, Can.
SOURCE: Alimentary Pharmacology and Therapeutics (2006), 23(8), 1179-1187
CODEN: APTHEN; ISSN: 0269-2813
PUBLISHER: Blackwell Publishing Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Background The effectiveness of proton pump inhibitors is influenced by meals and administration time. Aim To compare the effects on **intragastric acidity** of times of dosing of **tenatoprazole**, a novel imidazopyridine-based proton pump inhibitor with a prolonged plasma half-life. Methods This randomized three-period crossover study included 12 Helicobacter pylori-neg. healthy subjects, who received **tenatoprazole** 40 mg either fasting at 7.00 AM, fasting at 7.00 PM or fed at 9.30 PM for 7 days, with a 2-wk washout between periods. Twenty-four hour intragastric pH was monitored on day 7 of each period. Results On day 7, median 24-h pH was 4.7, 5.1 and 4.7 after breakfast, dinner and bedtime dosing, resp. ($P = 0.11$), whereas night-time pH was 4.2, 5.0 and 4.4 ($P = 0.13$). The mean 24-h percentage of time over pH 4 was 62, 72 and 64 after breakfast, dinner and bedtime dosing, resp. (N.S.), and 54, 68 and 56 during night-time ($P = 0.06$). Nocturnal acid breakthrough incidence decreased from 100% at baseline to 83%, 55% and 75% after 7.00 AM, 7.00 PM and 9.30 PM dosing, resp. ($P = 0.18$), and its mean duration dropped from 6.2 to 2.8, 1.0 and 2.2 h, resp. ($P < 0.05$). Conclusion Seven-day administration of **tenatoprazole** provides a prolonged duration of acid suppression, especially during the night-time, with little effect of food or time of dosing.
CC 1 (Pharmacology)
ST **tenatoprazole intragastric acidity** pharmacokinetics
IT INDEXING IN PROGRESS
IT Drug targets
(imidazopyridine-based proton pump inhibitor **tenatoprazole** inhibited **intragastric acidity** during fasting morning, fasting evening and fed bedtime in healthy Caucasian, Asian and African-American volunteer)
IT Transport proteins
(proton pump; imidazopyridine-based proton pump inhibitor **tenatoprazole** inhibited **intragastric acidity** during fasting morning, fasting evening and fed bedtime in healthy Caucasian, Asian and African-American volunteer)
IT Human
Human groups
Pharmacodynamics
(**tenatoprazole** inhibited **intragastric acidity** during fasting morning, fasting evening and fed bedtime in healthy Caucasian, Asian and African-American volunteer)
IT Pharmacokinetics

(**tenatoprazole** showed less steep slope of ascending curve to Cmax at fed bedtime state compared to fasting morning and evening states translating into higher Tmax in healthy Caucasian, Asian and African-American volunteer)

REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 2 OF 7 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2006:136566 HCAPLUS
DOCUMENT NUMBER: 144:357280
TITLE: Characterization of the inhibitory activity of **tenatoprazole** on the gastric H+,K+-ATPase in vitro and in vivo
AUTHOR(S): Shin, Jai Moo; **Homerin, Michel**; Domagala, Florence; **Ficheux, Herve**; Sachs, George
CORPORATE SOURCE: Department of Physiology and Medicine, David Geffen School of Medicine, University of California at Los Angeles, Los Angeles, CA, USA
SOURCE: Biochemical Pharmacology (2006), 71(6), 837-849
CODEN: BCPCA6; ISSN: 0006-2952
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB **Tenatoprazole** is a prodrug of the proton pump inhibitor (PPI) class, which is converted to the active sulfenamide or sulfenic acid by acid in the secretory canaliculus of the stimulated parietal cell of the stomach. This active species binds to luminally accessible cysteines of the gastric H+,K+-ATPase resulting in disulfide formation and acid secretion inhibition. **Tenatoprazole** binds at the catalytic subunit of the **gastric acid** pump with a stoichiometry of 2.6 nmol mg-1 of the enzyme in vitro. In vivo, maximum binding of **tenatoprazole** was 2.9 nmol mg-1 of the enzyme at 2 h after IV administration. The binding sites of **tenatoprazole** were in the TM5/6 region at Cys813 and Cys822 as shown by tryptic and thermolysin digestion of the ATPase labeled by **tenatoprazole**. Decay of **tenatoprazole** binding on the gastric H+,K+-ATPase consisted of two components. One was relatively fast, with a half-life 3.9 h due to reversal of binding at cysteine 813, and the other was a plateau phase corresponding to ATPase turnover reflecting binding at cysteine 822 that also results in sustained inhibition in the presence of reducing agents in vitro. The stability of inhibition and the long plasma half-life of **tenatoprazole** should result in prolonged inhibition of acid secretion as compared to omeprazole. Further, the bioavailability of **tenatoprazole** was two-fold greater in the (S)-**tenatoprazole** sodium salt hydrate form as compared to the free form in dogs which is due to differences in the crystal structure and hydrophobic nature of the two forms.

CC 63-5 (Pharmaceuticals)
Section cross-reference(s): 1
ST **tenatoprazole** prodrug antacid **gastric acid** stomach hydrogen potassium ATPase
IT Antacids
Crystal structure
Drug bioavailability
Hydrophobicity
Solubility
Stomach
(characterization of inhibitory activity of **tenatoprazole** on gastric H+,K+-ATPase in vitro and in vivo)
IT Transport proteins

RL: BSU (Biological study, unclassified); BIOL (Biological study)
(hydrogen ion potassium pump; characterization of inhibitory activity of **tenatoprazole** on gastric H+,K+-ATPase in vitro and in vivo)

IT Stomach
(parietal cell; characterization of inhibitory activity of **tenatoprazole** on gastric H+,K+-ATPase in vitro and in vivo)

IT Drug delivery systems
(prodrugs; characterization of inhibitory activity of **tenatoprazole** on gastric H+,K+-ATPase in vitro and in vivo)

IT **Gastric acid**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(secretion, inhibitors; characterization of inhibitory activity of **tenatoprazole** on gastric H+,K+-ATPase in vitro and in vivo)

IT 113712-98-4 705968-86-1, (S)-**Tenatoprazole** 705968-89-4
871567-50-9
RL: PKT (Pharmacokinetics); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(characterization of inhibitory activity of **tenatoprazole** on gastric H+,K+-ATPase in vitro and in vivo)

IT 881235-03-6
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(characterization of inhibitory activity of **tenatoprazole** on gastric H+,K+-ATPase in vitro and in vivo)

REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 3 OF 7 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:1335598 HCAPLUS
DOCUMENT NUMBER: 144:57370
TITLE: Preparation of sodium salt of S-**tenatoprazole** monohydrate for therapeutic application
INVENTOR(S): Cohen, Avraham; **Schutze, Francois**; **Charbit, Suzy**; Martinet, Frederic; **Ficheux, Herve**; **Homerin, Michel**
PATENT ASSIGNEE(S): Sidem Pharma S.A., Luxembourg
SOURCE: Fr. Demande, 19 pp.
CODEN: FRXXBL
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
FR 2871800	A1	20051223	FR 2004-6617	20040617
WO 2006005853	A1	20060119	WO 2005-FR1528	20050617

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

EP 1664044 A1 20060607 EP 2005-778749 20050617
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK, BA, HR, IS, YU
PRIORITY APPLN. INFO.: FR 2004-6617 A 20040617
WO 2005-FR1528 W 20050617

AB Sodium salt monohydrate of s-**tenatoprazole** is prepared for the treatment of digestive disorders. S-(-)-**tenatoprazole** (preparation given) was reacted with sodium hydroxide at 60° and the oil thus obtained was separated and purified to obtained sodium salt of S-(-)-**tenatoprazole** monohydrate, yield >90%.

IC ICM C07D471-04
ICS A61K031-4439; A61P001-00; C07D213-64; C07D233-96

CC 63-5 (Pharmaceuticals)
Section cross-reference(s): 28

ST sodium **tenatoprazole** monohydrate therapeutic prepn

IT Disease, animal
(digestion disorder; preparation of sodium salt of S-**tenatoprazole** monohydrate for therapeutic application)

IT Digestion, biological
(disease; preparation of sodium salt of S-**tenatoprazole** monohydrate for therapeutic application)

IT Hemorrhage
(gastric; preparation of sodium salt of S-**tenatoprazole** monohydrate for therapeutic application)

IT Digestive tract, disease
(gastroesophageal reflux; preparation of sodium salt of S-**tenatoprazole** monohydrate for therapeutic application)

IT Stomach, disease
(hemorrhage; preparation of sodium salt of S-**tenatoprazole** monohydrate for therapeutic application)

IT **Gastric acid**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(secretion, inhibitors; preparation of sodium salt of S-**tenatoprazole** monohydrate for therapeutic application)

IT Drug delivery systems
(tablets, compressed; preparation of sodium salt of S-**tenatoprazole** monohydrate for therapeutic application)

IT 113713-24-9 773892-01-6 871567-50-9, S-(-)-**Tenatoprazole** sodium monohydrate
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of sodium salt of S-**tenatoprazole** monohydrate for therapeutic application)

IT 705968-86-1P, S-(-)-**Tenatoprazole**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of sodium salt of S-**tenatoprazole** monohydrate for therapeutic application)

IT 9004-32-4, Carboxymethylcellulose 9004-34-6, Cellulose, biological studies 74811-65-7, Croscarmellose sodium
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of sodium salt of S-**tenatoprazole** monohydrate for therapeutic application)

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 4 OF 7 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:1115210 HCAPLUS
DOCUMENT NUMBER: 144:141930

TITLE: Effect on intragastric pH of a PPI with a prolonged plasma half-life: comparison between **tenatoprazole** and esomeprazole on the duration of acid suppression in healthy male volunteers

AUTHOR(S): Hunt, Richard H.; Armstrong, David; James, Cindy; Chowdhury, Sadat K.; Yuan, Yuhong; Fiorentini, Paola; **Taccoen, Alain**; Cohen, Patrick

CORPORATE SOURCE: Division of Gastroenterology, McMaster University Medical Centre, Hamilton, ON, Can.

SOURCE: American Journal of Gastroenterology (2005), 100(9), 1949-1956
CODEN: AJGAAR; ISSN: 0002-9270

PUBLISHER: Blackwell Publishing, Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB OBJECTIVE: To compare the inhibitory effect of a novel proton pump inhibitor (PPI), **tenatoprazole** 40 mg once daily, with esomeprazole 40 mg once daily on **intragastric acidity**. METHODS: A randomized, investigator-blind, two-way, crossover study was conducted in 30 healthy Helicobacter pylori neg. male volunteers. **Tenatoprazole** 40 mg or esomeprazole 40 mg was administered once daily for 7 consecutive days with a 4-wk washout period between treatments. Ambulatory 24-h intragastric pH was recorded at baseline, after 7 days' treatment, and 3 and 5 days after treatment was stopped. RESULTS: At presumed steady-state (day 7), median 24-h pH values were 5.02 and 4.79 for **tenatoprazole** and esomeprazole, resp. There was a significant difference between **tenatoprazole** and esomeprazole during the nocturnal period when mean pH was 4.64 ± 0.67 vs. 3.61 ± 0.90, resp. ($p < 0.0001$), as well as a significantly higher mean percentage of time with pH >4 on **tenatoprazole** (72.5 ± 14.9 vs 62.2 ± 13.6, $p < 0.0001$). The effect of **tenatoprazole** was still present 5 days after treatment withdrawal especially during the night-time. The mean area under the plasma concentration-time curve and elimination half-time was significantly higher in the **tenatoprazole** group as compared with the esomeprazole group. CONCLUSION: **Tenatoprazole** 40 mg daily provides a prolonged duration of acid suppression and a shorter nocturnal acid breakthrough in healthy volunteers, even after stopping the drug. Thus, **tenatoprazole** may provide greater clin. efficacy for patients in whom a once daily PPI is ineffective. Further studies are indicated.

CC 1-2 (Pharmacology)

ST **intragastric acidity** proton pump inhibitor **tenatoprazole** esomeprazole pharmacokinetics safety; pH acid suppression

IT Pharmacokinetics
(PPI **tenatoprazole** showed high area under plasma concentration and elimination half-life compared to esomeprazole and provide prolonged duration of acid suppression and shorter nocturnal acid breakthrough in healthy male volunteers)

IT **Acidity**
(**intragastric; tenatoprazole** 40 mg daily provide prolonged duration of acid suppression and shorter nocturnal acid breakthrough compared to esomeprazole in healthy male volunteers)

IT Human
(proton pump inhibitor **tenatoprazole** 40 mg daily provide prolonged duration of acid suppression and shorter nocturnal acid breakthrough compared to esomeprazole in healthy male volunteers)

IT Transport proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(proton pump; proton pump inhibitor **tenatoprazole** 40 mg daily

provide prolonged duration of acid suppression and shorter nocturnal acid breakthrough compared to esomeprazole in healthy male volunteers)

IT pH
(**tenatoprazole** 40 mg daily provide prolonged duration of acid suppression and shorter nocturnal acid breakthrough compared to esomeprazole in healthy male volunteers)

IT 113712-98-4, **Tenatoprazole** 119141-88-7, Esomeprazole
RL: ADV (Adverse effect, including toxicity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(proton pump inhibitor **tenatoprazole** 40 mg daily provide prolonged duration of acid suppression and shorter nocturnal acid breakthrough compared to esomeprazole in healthy male volunteers)

REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 5 OF 7 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:329705 HCAPLUS
DOCUMENT NUMBER: 142:441631
TITLE: A comparative study of the early effects of **tenatoprazole** 40 mg and esomeprazole 40 mg on intragastric pH in healthy volunteers
AUTHOR(S): Galmiche, J. P.; Sacher-Huvelin, S.; Des Varannes, S. Bruley; Vavasseur, F.; **Taccoen, A.**; Fiorentini, P.; **Homerin, M.**
CORPORATE SOURCE: CIC-INSERM-CHU de Nantes, Toussus-le-Noble, Fr.
SOURCE: Alimentary Pharmacology and Therapeutics (2005), 21(5), 575-582
CODEN: APTHEN; ISSN: 0269-2813
PUBLISHER: Blackwell Publishing Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Background: **Tenatoprazole** is a novel proton pump inhibitor with a seven-hour plasma half-life. Aim: To compare the effects of **tenatoprazole** 40 mg and esomeprazole 40 mg on **intragastric acidity** during the first 48 h in healthy volunteers. Methods: This randomized two-period crossover study included 24 Helicobacter Pylori-neg. subjects; **tenatoprazole** 40 mg or esomeprazole 40 mg daily were given before breakfast for two consecutive days, with a 2-wk wash-out between the administration periods. Intragastric pH was monitored for 48 h. Results: Over 48 h, **tenatoprazole** 40 mg exerted a more potent acid inhibition than esomeprazole 40 mg (median pH: 4.3 vs. 3.9, $P < 0.08$; per cent of time above pH 4: 57% vs. 49%, $P < 0.03$; proportion of subjects with at least half of the time above pH 4: 71% vs. 46%). These differences resulted from better night-time acid control with **tenatoprazole** 40 mg than esomeprazole 40 mg (first night median pH: 4.2 vs. 2.9, $P < 0.0001$; second night: 4.5 vs. 3.2, $P < 0.0001$). The duration of nocturnal acid breakthroughs was significantly reduced during both nights. In contrast, no significant difference was detected during the daytime periods between both regimens. Conclusion: Over the first 48 h, **tenatoprazole** 40 mg achieves a better overall and night-time control of gastric pH than esomeprazole 40 mg. The translation of better early control of acidity into clin. benefits deserves further studies.

CC 1-9 (Pharmacology)

ST **tenatoprazole** esomeprazole **intragastric acidity** proton pump inhibitor

IT Transport proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(proton pump; proton pump inhibitor, T40 and E40 was well tolerated, suppressed acid production, where T40 was more potent than E40 in better overall night-time control with reduced nocturnal acid break through in

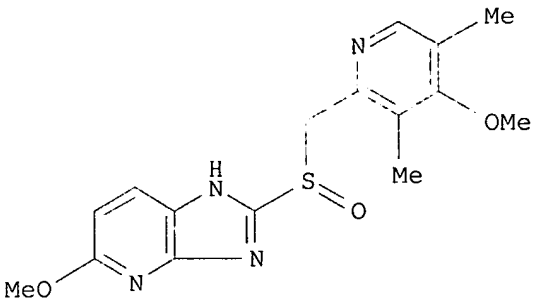
H.pylori neg. healthy human)
IT Human
Stomach
(**tenatoprazole** 40 mg and esomeprazole 40 mg was well tolerated, suppressed acid production, where T40 was more potent than E40 in better overall night-time control with reduced nocturnal acid break through in H.pylori neg. healthy human)
IT 113712-98-4, **Tenatoprazole** 119141-88-7, Esomeprazole
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**tenatoprazole** 40 mg and esomeprazole 40 mg was well tolerated, suppressed acid production, where T40 was more potent than E40 in better overall night-time control with reduced nocturnal acid break through in H.pylori neg. healthy human)
REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 6 OF 7 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:492326 HCAPLUS
DOCUMENT NUMBER: 141:54339
TITLE: **Tenatoprazole** enantiomer with improved pharmacokinetic behavior, and its therapeutic application in the treatment of digestive pathologies
INVENTOR(S): **Schutze, Francois; Charbit, Suzy; Ficheux, Herve; Homerin, Michel; Taccoen, Alain**; Cohen, Avraham
PATENT ASSIGNEE(S): Negma Gild, Fr.
SOURCE: Fr. Demande, 15 pp.
CODEN: FRXXBL
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
FR 2848555	A1	20040618	FR 2002-15949	20021216
FR 2848555	B1	20060728		
CA 2509899	AA	20040722	CA 2003-2509899	20031216
WO 2004060891	A1	20040722	WO 2003-FR3746	20031216
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2003300627	A1	20040729	AU 2003-300627	20031216
EP 1572692	A1	20050914	EP 2003-814481	20031216
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
BR 2003017328	A	20051108	BR 2003-17328	20031216
CN 1726214	A	20060125	CN 2003-80106267	20031216
JP 2006513230	T2	20060420	JP 2004-564280	20031216
US 2005119298	A1	20050602	US 2004-507485	20040913
US 7034038	B2	20060425		
NO 2005002798	A	20050704	NO 2005-2798	20050609

PRIORITY APPLN. INFO.: FR 2002-15949 A 20021216
WO 2003-FR3746 W 20031216

GI



I

AB The invention relates to the (-)-enantiomer of **tenatoprazole**, i.e., (-)-I, or (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridyl)methyl]sulfinyl]imidazo[4,5-b]pyridine. This enantiomer has improved pharmacokinetic properties relative to racemic I, allowing a posol. of only one dose of drug per day in indicated usages. (-)-I is applicable to treatment of digestive pathologies. Claims cover (-)-I and salts, preparation of (-)-I by chiral chromatog. of the racemate, compns. containing (-)-I and salts, particularly the Na, K, Li, Mg, and Ca salts, and the use of these compds. for treatment of a variety of specific conditions, or for inhibition of acid secretion. For instance, separation of 2 g (±)-I on a 265+110 mm ChiralPak column containing an amylose tris[(S)-α-methylbenzylcarbamate] stationary phase at ambient temperature gave (-)-I. Pharmacokinetic studies in Caucasians show that a mutation of cytochrome 2C19 gives rise to fast and slow metabolizers of I, which leads to plasma accumulation of (+)-I in CYP2C19*2/*2-homozygous slow metabolizers, and a higher proportion of (-)-I in CYP2C19*1/*1-homozygous fast metabolizers. It appears that (+)-I is metabolized predominantly by CYP2C19, whereas (-)-I is metabolized by 2 routes, CYP2C19 and CYP3A4. Thus, therapy with (-)-I offers the advantages of reduced variability between patients, better utilization, longer mean residence time, and reduced potential for drug interaction by compensation for potential CYP2C19 blockage. (-)-I has a plasmatic half-life of 10-12 h at 20-80 mg doses, whereas (±)-I has a half-life of 7 h at 20 mg and 9 h at 80 mg.

IC ICM C07D471-04
ICS A61K031-4439; A61P001-00

CC 28-9 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1, 63

ST **tenatoprazole** enantiomer prepn pharmacokinetics metab CYP2C19 CYP3A4; antiulcer treatment digestive pathol resoln **tenatoprazole** enantiomer prepn

IT Esophagus, disease
(Barrett's syndrome, treatment; preparation of **tenatoprazole** enantiomer with improved pharmacokinetic behavior, for treatment of digestive disorders)

IT Pancreas, neoplasm
(Zollinger-Ellison syndrome, treatment; preparation of **tenatoprazole** enantiomer with improved pharmacokinetic behavior, for treatment of digestive disorders)

IT Antibiotics
(coadministration with; preparation of **tenatoprazole** enantiomer with improved pharmacokinetic behavior, for treatment of digestive

disorders)
IT Helicobacter pylori
(cotreatment of infection with using antibiotics and; preparation of **tenatoprazole** enantiomer with improved pharmacokinetic behavior, for treatment of digestive disorders)
IT Hemorrhage
(digestive tract, treatment; preparation of **tenatoprazole** enantiomer with improved pharmacokinetic behavior, for treatment of digestive disorders)
IT Ulcer
(duodenal, treatment; preparation of **tenatoprazole** enantiomer with improved pharmacokinetic behavior, for treatment of digestive disorders)
IT Intestine, disease
(duodenum, ulcer, treatment; preparation of **tenatoprazole** enantiomer with improved pharmacokinetic behavior, for treatment of digestive disorders)
IT Digestive tract, disease
(gastroesophageal reflux, treatment; preparation of **tenatoprazole** enantiomer with improved pharmacokinetic behavior, for treatment of digestive disorders)
IT Digestive tract, disease
(hemorrhage, treatment; preparation of **tenatoprazole** enantiomer with improved pharmacokinetic behavior, for treatment of digestive disorders)
IT Antiulcer agents
Human
(preparation of **tenatoprazole** enantiomer with improved pharmacokinetic behavior, for treatment of digestive disorders)
IT Transport proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(proton pump, inhibitors; preparation of **tenatoprazole** enantiomer with improved pharmacokinetic behavior, for treatment of digestive disorders)
IT **Gastric acid**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(secretion, inhibitors, treatment; preparation of **tenatoprazole** enantiomer with improved pharmacokinetic behavior, for treatment of digestive disorders)
IT Digestive tract, disease
(treatment; preparation of **tenatoprazole** enantiomer with improved pharmacokinetic behavior, for treatment of digestive disorders)
IT 113712-98-4, (±)-**Tenatoprazole**
RL: PEP (Physical, engineering or chemical process); PKT (Pharmacokinetics); PYP (Physical process); BIOL (Biological study); PROC (Process)
(chromatog. resolution; preparation of **tenatoprazole** enantiomer with improved pharmacokinetic behavior, for treatment of digestive disorders)
IT 329736-03-0, Cytochrome CYP3A4 330589-90-7, Cytochrome CYP2C19
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(genetics and metabolism of **tenatoprazole** enantiomers by; preparation of **tenatoprazole** enantiomer with improved pharmacokinetic behavior, for treatment of digestive disorders)
IT 705968-86-1P 705968-89-4P, (-)-**Tenatoprazole** sodium salt
705968-92-9P, (-)-**Tenatoprazole** potassium salt 705968-95-2P,
(-)-**Tenatoprazole** lithium salt 705968-98-5P, (-)-
Tenatoprazole magnesium salt 705968-99-6P, (-)-
Tenatoprazole calcium salt
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); SPN (Synthetic

preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of **tenatoprazole** enantiomer with improved pharmacokinetic behavior, for treatment of digestive disorders)
IT 705969-00-2
RL: PKT (Pharmacokinetics); BIOL (Biological study)
(preparation of **tenatoprazole** enantiomer with improved pharmacokinetic behavior, for treatment of digestive disorders)
REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 7 OF 7 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:378286 HCAPLUS
DOCUMENT NUMBER: 141:360444
TITLE: **Tenatoprazole**, a novel proton pump inhibitor with a prolonged plasma half-life: effects on intragastric pH and comparison with esomeprazole in healthy volunteers
AUTHOR(S): Galmiche, J. P.; des Varannes, S. Bruley; Ducrotte, P.; Sacher-Huvelin, S.; Vavasseur, F.; **Taccoen, A.**; Fiorentini, P.; **Homerin, M.**
CORPORATE SOURCE: CIC-INSERM, CHU de Nantes, Nantes, Fr.
SOURCE: Alimentary Pharmacology and Therapeutics (2004), 19(6), 655-662
CODEN: APTHEN; ISSN: 0269-2813
PUBLISHER: Blackwell Publishing Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Background: Proton pump inhibitors control **gastric acidity** better during the day than at night, when nocturnal acid breakthrough can occur. **Tenatoprazole** is a novel proton pump inhibitor with a seven-fold longer plasma half-life. Aim: To compare the effects of **tenatoprazole** 20 mg (T20), **tenatoprazole** 40 mg (T40) and esomeprazole 40 mg (E40) on **intragastric acidity** in healthy volunteers. Methods: This randomized, three-period, cross-over study enrolled 18 Helicobacter pylori-neg. volunteers, who received E40, T20 and T40 once daily for 7 days with a 14-day washout between periods. Twenty-four-hour gastric pH monitoring was performed on day 7. Serum gastrin was assessed on day 8. Results: T40 induced a more potent acid inhibition than T20 (24-h median pH: 4.6 vs. 4.0, $P < 0.01$; daytime: 4.5 vs. 3.9, $P < 0.01$; night-time: 4.7 vs. 4.1, $P < 0.05$). T40 was more potent than E40 (24-h median pH: 4.6 vs. 4.2, $P < 0.05$; night-time: 4.7 vs. 3.6, $P < 0.01$); the pH > 4 holding time was higher during the night for T40 than for E40: 64.3% vs. 46.8%, $P < 0.01$; the nocturnal acid breakthrough duration was significantly shorter for T40 than for E40. No significant gastrin increase was observed and all drugs were well tolerated. Conclusion: T40 is significantly more potent than T20 and E40 during the night. The therapeutic relevance of this pharmacol. advantage deserves further study.
CC 1-9 (Pharmacology)
ST **tenatoprazole** esomeprazole **gastric acid** secretion proton pump inhibitor stomach
IT Rhythm, biological
(circadian; **tenatoprazole** and esomeprazole were well tolerated and highly effective in controlling intragastric pH with no significant gastrin increase, but T40 was more potent than T20 and E40 during night in healthy human)
IT Rhythm, biological
(nocturnal; **tenatoprazole** and esomeprazole were well tolerated and highly effective in controlling intragastric pH with no

significant gastrin increase, but T40 was more potent than T20 and E40 during night in healthy human)

IT Drug targets
(proton pump inhibitors **tenatoprazole** and esomeprazole were well tolerated and highly effective in controlling intragastric pH with no significant gastrin increase, but T40 was more potent than T20 and E40 during night in healthy human)

IT Transport proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(proton pump, inhibitor; **tenatoprazole** and esomeprazole were well tolerated and highly effective in controlling intragastric pH with no significant gastrin increase, but T40 was more potent than T20 and E40 during night in healthy human)

IT **Gastric acid**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(secretion, inhibitors; **tenatoprazole** and esomeprazole were well tolerated and highly effective in controlling intragastric pH with no significant gastrin increase, but T40 was more potent than T20 and E40 during night in healthy human)

IT Human
pH
(**tenatoprazole** and esomeprazole were well tolerated and highly effective in controlling intragastric pH with no significant gastrin increase, but T40 was more potent than T20 and E40 during night in H. pylori-neg. healthy human)

IT Antiulcer agents
Stomach
(**tenatoprazole** and esomeprazole were well tolerated and highly effective in controlling intragastric pH with no significant gastrin increase, but T40 was more potent than T20 and E40 during night in healthy human)

IT 119141-88-7, Esomeprazole
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**tenatoprazole** and esomeprazole were well tolerated and highly effective in controlling intragastric pH with no significant gastrin increase, but T40 was more potent than T20 and E40 during night in H. pylori-neg. healthy human)

IT 9002-76-0, Gastrin
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**tenatoprazole** and esomeprazole were well tolerated and highly effective in controlling intragastric pH with no significant gastrin increase, but T40 was more potent than T20 and E40 during night in healthy human)

IT 113712-98-4, **Tenatoprazole**
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**tenatoprazole** with prolonged plasma half-life and esomeprazole were well tolerated, highly effective in controlling intragastric pH with no significant gastrin increase, but T40 was more potent than T20, E40 during night in healthy human)

REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT